result in a model of Alzheimer's disease, many transgenic animals have been made. Some of the animals produced have some useful phenotypes. For example, mice (described in WO 95/11968) expressing a form of APP751 having the Swedish mutation produce moderately elevated levels of Aβ, and mice (described in U.S. Patent No. 5,387,742) expressing APP751 form Aβ deposits in the brain of the mice which at best are similar only to immature preamyloid deposits seen in humans. The deposits described in the '742 patent do not stain with Congo red. Although there were numerous theories about which factors might be important for producing the most useful animal models of Alzheimer's disease, prior to applicants' discovery that high levels of the expression products recited in the claims are determinants for obtaining transgenic animals producing plaques closely related to those found in Alzheimer's disease, it was not known which factors would in fact turn out to be important.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-20, 22-26 and 28-56 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

Under 35 U.S.C. § 112, first paragraph, applicants are required to describe the claimed invention in sufficient detail to enable those of skill in the art to make and use it without the need for undue experimentation. Applicants submit that this has been done. The claims use a transgenic mouse expressing an APP-related construct, where one or more the recited expression products is expressed at a specific levels. Applicant submits that the production of such mice by those of skill in the art would not require undue experimentation. The claimed assay is useful for identifying compounds that may affect Alzheimer's disease. Such compounds would be of interest to those in the art as, for example, lead compounds for therapeutics. Numerous publications are cited in the specification both describe procedures for detecting and measuring

the claimed markers and indicate that those of skill in the art would know how to do so. Applicants believe that there is no question that the detection of such markers can be accomplished without the need for undue experimentation, and that the results of such an assay would have been considered by those of skill in the art to be useful and relevant to Alzheimer's disease and the discovery of potential therapeutics.

The present rejection appears to be based on two main rationales, neither of which ultimately supports the rejection. First, that the specification must point to specific constructs that will express Aβ-related expression products at the levels recited in the claims. Second, that it would require undue experimentation to obtain transgenic mice with useful phenotypes.

A. Applicants initially note that the rejection overall is premised on an apparent disconnection (in the rejection) between the physical constructs recited in the claims and the phenotype recited in the claims. The rejection notes that the claimed constructs will not produce the required expression (noting, for example, the transgenic mice disclosed in the prior art which do not produce the recited levels). The implication is that constructs that fail to produce the required expression level are encompassed by the claims. However, this is not the case. The expression level recited in the claims is a limitation on the claimed mice. That is, only those mice which produce the required level of expression, regardless of the construct present, are encompassed by the claims. There is no requirement that all of the physical constructs **recited** in the claims be shown to produce, be capable of producing, or be enabled for production of, the recited level of Aβ-related expression products. The recited level of expression is a limitation too, and limits the transgenic mice to those that have the **combination** of a construct within the scope of constructs recited **and** the recited level of production of Aβ-related expression products.

The non-productive animals referred to in the rejection that contain certain constructs are excluded from the claims by virtue of the expression limitation.

A related rationale also apparent in the rejection is the implication that failure of prior transgenic mice to express Aβ-related expression products at the level recited in the present claims establishes that achieving such expression levels would require undue experimentation. However, applicants note that the evidence of the art does not clearly support this premise. For example, there is no evidence that high levels of expression of Aβ-related expression products were sought in the prior art animals. In some cases there is evidence to the contrary. This limits the significance of these publications as "evidence" that such expression levels will be difficult to achieve.

Lannfelt *et al.*, *Behavioural Brain Research* 57:207-213 (1993), does not support the rejection as suggested in the Office Action. The cited portions of Lannfelt *et al.* are in a section where the authors--confronted with the prior, failed attempts to produce APP animal models of Alzheimer's disease--speculate on possible reasons for this failure. There is no indication that any of these speculations are accurate. Such speculation can hardly serve as the basis for establishing that they were actually a problem in the art at the time. Furthermore, Lannfelt *et al.* does not say anything about the ease or difficulty of achieving high levels of expression (the apparent point of citing Lannfelt *et al.*). Rather, Lannfelt *et al.* merely notes (page 210, second column, fourth paragraph, lines 11-12) that expression levels of the APP transgene were low in the failed animals.[1] Lannfelt *et al.* does not suggest that high levels of expression would be difficult to achieve.

[1] In fact, this supports patentability of the present mice since it is applicants' discovery that high levels of expression lead to transgenic mice having useful phenotypes (see discussion below).

Applicants submit that, at the time the priority date of the present application, that it would not have required undue experimentation to produce the claimed transgenic mice having the level of expression required by the claims. There is no evidence on the record establishing such difficulty.[2]

B. Applicants submit that the level of expression of Aβ-related expression products as claimed is an important determinant of obtaining useful phenotypes in mice transgenic for APP constructs. Sirinathsinghji, *Curr. Res. Alzheimer's Disease* 3:47-56 (1998) (of record), discusses three successful transgenic mouse models of Alzheimer's disease. Sirinathsinghji describes PDAPP mice (pages 48-49; Games *et al.*, *Nature* 373:523-527 (1995) (of record)) and Hsiao mice (page 49; Hsiao *et al.*, *Science* 274:99-102 (1996) (of record)), both of which produce significant phenotypes that are similar to those seen in Alzheimer's disease. In both cases, Sirinathsinghji emphasizes that the level of expression of the transgene is high. Sirinathsinghji also describes another transgenic mouse line produced by Novartis (page 49; Sommer *et al.*, *Soc. Neurosci.* 26:Abstract 19.9:25 (1996), a copy of which is submitted with this Amendment), which has a high level of production of Aβ-related expression products (consistent with the present claims) and exhibits significant characteristics that are similar to characteristics observed in Alzheimer's disease, including plaques that stain with Congo red. Sirinathsinghji summarizes the significance of these results by noting (page 47, first paragraph) that it is now clear that mutations associated with Alzheimer's disease all lead to increased levels of Aβ and that results with mice overexpressing Aβ is consistent with, and confirms, the importance of Aβ production in the development of Alzheimer's disease. In this regard, Sirinathsinghji notes that all three mouse models show region-specific deposition of Aβ plaques.

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[2] The Office Action alleges (page 16) that there are "deficiencies" in the specification but fails to identify them.

Mucke et al., *J. Neuroscience* 20(1):4050-4058 (2000) (a copy of which is enclosed), describe at least six mouse lines harboring constructs and exhibiting Aβ expression as claimed.[3] Mucke et al. analyzed the correlation of high Aβ levels in young mice on synaptophysin-immunoreactive (SYN-IR) presynaptic terminals in brain tissue.[4] A significant negative correlation was found between Aβ levels in young mice and synaptophysin-immunoreactive (SYN-IR) presynaptic terminals in brain tissue (see first partial paragraph on page 4056 and Figure 9). No correlation was seen between APP levels and SYN-IR presynaptic terminals (see sentences bridging pages 4055 and 4056 and Figure 8). Thus, as emphasized in the present application and claims, the level of Aβ levels in young mice is an important determinate of obtaining useful phenotypes in mice transgenic for APP constructs.

Mucke et al. also shows that mice expressing Aβ at high levels can be produced reliably and repeatedly. Mucke et al. produced transgenic mice having high levels of Aβ expression using three different constructs (see Figure 3). The results of Mucke et al. also support enablement because they show that prior transgenic animals with similar constructs but poor phenotypes are not evidence that the present high expression levels are precluded for a particular construct. In particular, Mucke et al. obtained different transgenic mice using the same construct but exhibiting a variety of expression levels (see Figure 3). The fact that mice with a variety of expression levels were obtained is not a problem since those of skill in the art would expect individual transgenic animals and lines of animals to exhibit a range of expression levels. Thus, Mucke et al. provides evidence that mice as claimed can be produced without the need for undue experimentation.

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[3] The mouse lines are I5, I63, H40, H6, J9, and J20 (see Figure 3).

[4] There is a good correlation between cognitive defects in Alzheimer's disease and loss of synaptophysin-immunoreactive presynaptic terminals. See Abstract and first paragraph in column two on page 4050 in Mucke et al.

Applicants again emphasize that a key distinction between prior transgenic animals carrying APP transgenes and the transgenic mice presently claimed is the expression level. Sirinathsinghji and Mucke et al. confirm applicants' discovery that this feature is correlated with transgenic mice having useful characteristics. Applicants submit that the mice of Hsiao and Novartis (see Sirinathsinghji) and of Mucke et al. are consistent with the importance of the level of expression.

C. It is submitted that the burdens on those of skill in the art wishing to obtain murine models of Alzheimer's disease are greatly reduced by applicants' discovery (as embodied in the present claims) since such artisans can focus on obtaining transgenic mice having the required level of expression of Aβ-related expression products and reasonably expect that they will have useful phenotypes. Although not every individual transgenic mouse produced will express Aβ-related expression products at the required level, a reasonable number will. Applicants submit that this is analogous to the issue in *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988), where the Federal Circuit found that the production of claimed monoclonal antibodies in only 2.3% of attempts to make such antibodies was an acceptable amount of experimentation. Significantly, in *Wands* the Federal Circuit was influenced by the fact that, in the relevant art, such efforts and rates of success were normal and expected. Applicants submit that, in the art of transgenic mice, a similar situation exists. It is common, and considered acceptable, that several attempts may be required to produce a transgenic mouse expressing a desired transgene. Such efforts are considered routine and a part of the art. Further, with the present invention the effort needed to produce useful transgenic mice that exhibit Alzheimer's-related plaques is greatly reduced since a determination can be made when the mice are two to four months of age (by measuring

expression levels of Aβ-related expression products) rather than waiting for up to two years for Alzheimer's-related plaques to develop.

D. The Office Action makes several arguments regarding the phenotype of the claimed animals and the correlation of these phenotypes to Alzheimer's disease. Applicants submit that the phenotypes recited in the claims are sufficiently related to Alzheimer's disease to make the claimed mice useful for the study of Alzheimer's disease and the assessment of potential therapeutics. It is clear that such use need not reach any arbitrary standard of accuracy. It is enough that those in the art would find the disclosed mice useful. This is analogous to the minimal requirements needed to establish utility of potentially therapeutic compounds. For example, the Federal Circuit has held that adequate proof of a pharmacological activity can be obtained by merely providing *in vitro* data which is suggestive of an activity *in vivo*. (*Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985). "Successful in vitro testing . . . [will lead to] . . . in vivo testing . . . thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an in vivo utility." *Id.* at 1051. Furthermore, data obtained from animal models clearly is adequate proof. *In re Krimmel* 292 F.2d 948 (C.C.P.A. 1961). The *Krimmel* court stated, "one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant contribution to the art even though it may eventually appear that the compound is without value in the treatment of humans." *Id.* at 953. Analogously, by providing transgenic mice producing markers known (or believed by those in the art) to be associated with Alzheimer's disease, those in the art are provided with a tool that they would consider useful for analysis and testing.[5] This is a sufficient use for the claimed mice to satisfy the requirements of 35 U.S.C. § 112, first paragraph.

[5] For example, those of skill in the art could use the claimed mice to identify lead compounds that could them be tested for therapeutic efficacy. There is no question that the mere identification of such lead compounds would be

E. Regarding the use of various markers recited in the claims, applicants note that the various markers are believed to be associated with Alzheimer's disease. Applicants have asserted this belief in the specification. Unless there is evidence to doubt this assertion, it must be accepted. Here, the rejection merely argues that there is no evidence that some of the markers are associated with Alzheimer's disease. This improperly puts the burden on applicants to show such an association when in fact it is the Patent Office that is burdened with showing that there is no such association. This has not been done and this aspect of the rejection fails for at least this reason.

Applicants also note that a belief that the markers are associated with Alzheimer's disease is enough to make the claimed method useful for those in the art. In the field of Alzheimer's disease, those in the art are interested in, and would find useful, any assay likely to be relevant to Alzheimer's disease. For such an important and devastating disease, the art cannot wait for certainty in assay and model before identifying potential therapeutics. As discussed above, it is clear that the claimed assay need not reach any arbitrary standard of accuracy. It is enough that those in the art would find the disclosed mice useful (see discussion of *Cross* and *Krimmel* above). By providing transgenic mice producing markers known (or believed by those in the art) to be associated with Alzheimer's disease, those in the art are provided with a tool that they would consider useful for analysis and testing. This is a sufficient use for the claimed assays using the recited markers to satisfy the requirements of 35 U.S.C. § 112, first paragraph.

F. In the case of the use of cells from the claimed transgenic mice, applicants note that such use merely represents an alternative use of the claimed mice. Applicants also note that the claims do not require that cells from the claimed mice have a particular phenotype themselves.

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considered highly useful by those in the field.

35 U.S.C. § 112 does not require this. Applicants submit that this aspect of the rejection is not germane to the present claims.

For all these reasons, applicants assert that the claims are enabled.

Rejections Under 35 U.S.C. § 102

1. Claims 1, 2, 5-20, 24-26, 28-30, 33-48, 51-53, and 56 were rejected under 35 U.S.C. § 102(a) as being anticipated by WO 95/11968. Applicants respectfully traverse this rejection.

A. For a rejection of claims to be properly founded under 35 U.S.C. §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 U.S.P.Q. 81 (Fed. Cir. 1986); *Scripps Clinic & Research Found v Genentech Inc*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991).

Regarding inherency, the Federal Circuit recently stated:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.
>
> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient. This modest flexibility in the rule that "anticipation" requires that every element of the claims appear in a single reference accommodates situations where the common knowledge of technologists is not recorded in the reference; that is, where technological facts are known to those in the field of the invention, albeit not known to judges.

Finnigan Corp. v. United States Int'l Trade Comm'n, 180 F.3d 1354, 1365 (Fed. Cir. 1999) (citations omitted).

A claim element is not "inherent" in the disclosure of a prior art reference unless extrinsic evidence clearly shows that missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Robertson*, 49 U.S.P.Q.2d 1949 (Fed. Cir. 1999).

B. WO 95/11968 discloses transgenic animals containing a construct encoding APP having the Swedish mutation. The present claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. WO 95/11968 does not disclose a transgenic mouse that produces these expression products at the required level. Thus, WO 95/11968 fails to disclose each and every feature of the claimed mice.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of WO 95/11968 because "the construct disclosed in [WO 95/11968] is also claimed by applicant," no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art.[6] The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of WO 95/11968 and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails.

It is also clear that those of skill in the art would not have recognized that the mice of WO 95/11968 would necessarily produce the claimed levels of expression. The Office Action

[6] This latter requirement recognizes that inherency doctrine is meant to apply "where common knowledge of technologists is not recorded in the reference." *Finnigan Corp. v. United States Int'l Trade Comm'n*, 180 F.3d 1354, 1365 (Fed. Cir. 1999). This is clearly not the case here where applicants discovered a new characteristic that produces more useful models.

itself supports this in the context of the rejection under 35 U.S.C. § 112, first paragraph. As the court in *Finnigan* made clear, inherency is intended to accommodate those situations where some unstated feature would be known by those of skill in the art to be present while the layperson may not.[7] This is not such a case. The claimed expression levels are not a part of the common knowledge of those of skill in the art and are not the kind of thing that would be recognized by those of skill in the art as an understood (but unstated) feature of the mice of WO 95/11968. Thus, the claimed expression levels are not inherent in the mice of WO 95/11968. For at least this reason, the present rejection fails.

The logic of the rejection appears to be based on the fallacy that the transgene construct used inherently results in a given set of characteristics (e.g. the expression levels of the claimed mice). First, it cannot be said that all of the mice disclosed in WO 95/11968 will have the required expression. There is no evidence that all of the mice will express the transgene,[8] and at least some of the transgenic mice will fail to express the transgene due to, for example, insertion site effects. The fact that not all of the mice of WO 95/11968 will have the required expression dooms the inherency argument. The Federal Circuit in *Glaxo v. Novapharm*, 52 F.3d 1043 (Fed. Cir. 1995), held that an inconsistent result precluded inherency. In *Glaxo*, a prior art process was *demonstrated* to sometimes produce the claimed form of a compound and to sometimes produce a different form of the compound. Because of this inconsistent result, the court rejected a claim of anticipation based on alleged inherent production of the claimed form of the compound.[9]

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[7] Such an accommodation is appropriate since the prior art is to be interpreted from the point of view of those of ordinary skill in the art.
[8] In fact, there is no evidence that *any* of the mice disclosed in WO 95/11968 will have the required expression.
[9] Thus, Glaxo illustrates the requirement that the feature at issue necessarily be present means that the feature must be present *of necessity* (that is, the feature must be present). This is what "necessarily" means in the inherency sense.

Here, as in *Glaxo*, the claimed characteristic (high expression mice; claimed form of compound) is not *necessarily* produced in the prior art process. Inherency fails in both cases.[10]

The expression level is a separate limitation from the construct, and some mice having a claimed construct may not have the claimed expression. That these facts preclude inherency while being consistent with enablement can easily be reconciled due to the different standards involved. Enablement requires only that undue experimentation not be required. As discussed above, the fact that only some of the mice made will have the claimed expression characteristics is acceptable under 35 U.S.C. § 112 where such a success rate is ordinary and expected in the field. Thus, the fact that some number of the transgenic mice produced may not have the claimed expression does not mean that undue experimentation is required to produce the claimed mice since mice having the required expression will be produced at a reasonable frequency (see discussion above). On the other hand, the transgenic mice as disclosed in WO 95/11968 will not *necessarily* exhibit the claimed expression (in the inherency sense), even assuming, arguendo, that *some* of the mice produced would happen to exhibit the claimed expression levels. Such a lower rate of "success"[11] at producing mice having the presently claimed expression levels, even if it occurred, does not rise to the level of inevitable appearance of the features at issue as required for inherency.

Accordingly, for all of the above reasons, WO 95/11968 fails to anticipate the claimed mice.

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[10] A recent decision by the United States District Court for the Northern District of California (Elan Pharmaceuticals, Inc. v. Mayo Foundation For Medical Education And Research, No. C 99-04464 WHA (N.D. Cal. June 15, 2000)(unreported)) involving commonly assigned patents drawn to transgenic rodents expressing the Swedish mutation of APP (U.S. Patent Nos. 5,612,486 and 5,850,003) applied *Glaxo* to prior art cited against the patent (a copy of the decision is submitted with this Amendment). This decision is being appealed.

[11] Such mice constitute a "success" only in hindsight based on applicants' discovery that such expression levels are useful.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in WO 95/11968. For this additional reason, WO 95/11968 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41.

2. Claims 1-20, 22, 23, 26, 29-50, 53, and 54 were rejected under 35 U.S.C. § 102(b) as being anticipated by WO 93/14200. Applicants respectfully traverse this rejection.

WO 93/14200 discloses transgenic animals containing constructs encoding, for example, APP770, APP751, and APP695, which serve as models of Alzheimer's disease. As noted above, the claims require that the transgenic mouse produce specific expression products. However, the only transgenic mouse disclosed in WO 93/14200 that produces the expression products at the required level (that is, the mouse having the combination cDNA/genomic DNA APP construct[12]) is specifically excluded from the claims. Thus, WO 93/14200 fails to disclose each and every feature of the claimed mice.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of WO 93/14200, no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of WO 93/14200[13] and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails. Applicants also submit that the arguments regarding inherency made with

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[12] The $A\beta_{tot}$, $A\beta_{1-42}$, APPα, APPβ, and Aβ-encoding mRNA expression of this mouse, which corresponds to the transgenic mouse described by Games *et al.*, is neither disclosed nor suggested in WO 93/14200.

[13] Other than the mouse with the disclaimed construct.

respect to WO 95/11968 apply equally to WO 93/14200, and that for those additional reasons, the present rejection fails.

Accordingly, WO 93/14200 fails to anticipate the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in WO 93/14200. For this additional reason, WO 93/14200 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41.

3. Claims 1-20, 22, 23, 26, 28-50, and 53-56 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,720,936. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,720,936 describes transgenic animals containing constructs encoding, for example, APP770, APP751, and APP695, which serve as models of Alzheimer's disease. As noted above, the claims require that the transgenic mouse produce specific expression products. However, the only transgenic mouse disclosed in U.S. Patent No. 5,720,936 that produces the expression products at the required level (that is, the mouse having the combination cDNA/genomic DNA APP construct[14]) is specifically excluded from the claims. Thus, U.S. Patent No. 5,720,936 fails to disclose each and every feature of the claimed mice.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of U.S. Patent No. 5,720,936, no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of U.S. Patent No.

[14] The $A\beta_{tot}$, $A\beta_{1-42}$, APPα, APPβ, and Aβ-encoding mRNA expression of this mouse, which corresponds to the transgenic mouse described by Games *et al.*, is neither disclosed nor suggested in U.S. Patent No. 5,720,936.

5,720,936[15] and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails. Applicants also submit that the arguments regarding inherency made with respect to WO 95/11968 apply equally to U.S. Patent No. 5,720,936, and that for those additional reasons, the present rejection fails.

Accordingly, U.S. Patent No. 5,720,936 fails to anticipate the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,720,936. For this additional reason, U.S. Patent No. 5,720,936 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41.

4. Claims 1, 2, 5-20, 24-26, 28, 29, 33-45, 51-53, and 56 were rejected under 37 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,604,102. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,604,102 discloses transgenic animals containing a construct encoding APP having the Swedish mutation. The present claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. U.S. Patent No. 5,604,102 does not disclose a transgenic mouse that produces these expression products at the required level. Thus, U.S. Patent No. 5,604,102 fails to disclose each and every feature of the claimed mice.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of U.S. Patent No. 5,604,102, no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would

[15] Other than the mouse with the disclaimed construct.

have been recognized by those of ordinary skill in the art. The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of U.S. Patent No. 5,604,102 and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails. Applicants also submit that the arguments regarding inherency made with respect to WO 95/11968 apply equally to U.S. Patent No. 5,604,102, and that for those additional reasons, the present rejection fails.

Accordingly, U.S. Patent No. 5,604,102 fails to anticipate the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,604,102. For this additional reason, U.S. Patent No. 5,604,102 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41.

5. Claims 1-20, 22, 23-26, and 28-56 were rejected under 35 U.S.C. § 102(f) because the applicant did not invent the claimed subject matter. Applicants respectfully traverse this rejection.

A. U.S. Patent No. 5,720,936 discloses transgenic animals containing constructs encoding, for example, APP770, APP751, and APP695, which serve as models of Alzheimer's disease. As noted above, the claims require that the transgenic mouse produce the expression products recited in the claims at specific levels. However, the only transgenic mouse disclosed in U.S. Patent No. 5,720,936 that produces these expression products at this level (that is, the mouse having the combination cDNA/genomic DNA APP construct[16]) is specifically excluded from the claims. Thus, U.S. Patent No. 5,720,936 fails to disclose each and every feature of the claimed mice.

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[16]The $A\beta_{tot}$, $A\beta_{1-42}$, APPα, APPβ, and Aβ-encoding mRNA expression of this mouse, which corresponds to the transgenic mouse described by Games *et al.*, is neither disclosed nor suggested in U.S. Patent No. 5,720,936.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of U.S. Patent No. 5,720,936, no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of U.S. Patent No. 5,720,936[17] and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails. Applicants also submit that the arguments regarding inherency made with respect to WO 95/11968 apply equally to U.S. Patent No. 5,720,936, and that for those additional reasons, the present rejection fails.

Accordingly, U.S. Patent No. 5,720,936 fails to anticipate the claimed mice and thus fails to show that applicants did not invent the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,720,936. For this additional reason, U.S. Patent No. 5,720,936 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41 and thus fails to show that applicants did not invent the claimed mice.

B. U.S. Patent No. 5,604,102 discloses transgenic animals containing a construct encoding APP having the Swedish mutation. The present claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. U.S. Patent No. 5,604,102 does not disclose a transgenic mouse that produces these

[17] Other than the mouse with the disclaimed construct.

expression products at the required level. Thus, U.S. Patent No. 5,604,102 fails to disclose each and every feature of the claimed mice.

While the rejection alleges that the features of the claimed mice are inherent in the transgenic mice of U.S. Patent No. 5,604,102, no *prima facie* case of inherency was established. Where the cited reference is silent about the asserted inherent characteristic, evidence must be presented to show that the missing descriptive matter is necessarily present and that this would have been recognized by those of ordinary skill in the art. The rejection provides no evidence that the claimed expression levels are *necessarily* present in the mice of U.S. Patent No. 5,604,102 and no evidence that those of ordinary skill in the art would have recognized this. For at least this reason, the present rejection fails. Applicants also submit that the arguments regarding inherency made with respect to WO 95/11968 apply equally to U.S. Patent No. 5,604,102, and that for those additional reasons, the present rejection fails.

Accordingly, U.S. Patent No. 5,604,102 fails to anticipate the claimed mice and thus fails to show that applicants did not invent the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,604,102. For this additional reason, U.S. Patent No. 5,604,102 does not anticipate claims 8, 10, 12, 14, 35, 37, 39, and 41 and thus fails to show that applicants did not invent the claimed mice.

Rejections Under 35 U.S.C. § 103

1. Claims 1, 4, 10-13 and 21-24 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,387,742, in view of Sasahara, et al., *Cell* 64:217-227 (1991); Mullen, et al., *Nature Genetics* 1:345-347 (1992); Chartier-Harlin, et al., *Nature* 353:844-846

(1991); and Hendriks, et al., *Nature Genetics* 1:218-221 (1992). Applicants respectfully traverse this rejection.

A. U.S. Patent No. 5,387,742 discloses transgenic mice expressing APP770, APP751, APP695, A42, A99, or A4i from the neural-specific enolase or metallothionein promoters. The '742 patent discloses that these mice exhibit deposits of β-amyloid peptide in brain tissue. The '742 patent also discloses that such mice can be used in an assay to determine if drugs can affect the amount and nature of deposits. The '742 patent fails to disclose or suggest any transgenic mouse producing the expression products recited in the claims at recited levels. The mice disclosed in the '742 patent exhibit only diffuse deposits of Aβ that do not stain with Congo red and neuronal soma and processes. The Aβ deposits of these mice were later characterized by Higgins *et al.*, *Annals New York Acad. Sci.* 695:224-227 (1993), of record, in the following passage:

> The deposits are about 5-30 μm in diameter and have a cotton-like appearance or occasionally a more dense morphology....The deposits appear extracellular and are structurally similar to those observed in brains of young adult [Down' syndrome] individuals, as well as to *immature pre*amyloid and small deposits in AD brain. (page 225; emphasis added)

Authentic AD plaques do not have a cotton-like appearance and immature preamyloid deposits in humans do not stain with Congo red. Significantly, Higgins *et al.* discloses that similar deposits are seen in non-transgenic mice (see Table 1). Consistent with the absence of authentic AD plaques in these mice, the '742 patent was allowed on the basis of observed behavioral changes in the mice.

Sasahara *et al.* disclose the platelet-derived growth factor B chain (PDGF-B) promoter. Sasahara *et al.* also disclose that the PDGF-B promoter preferentially expresses a heterologous

protein in brain tissue of a transgenic mouse. Sasahara *et al.* fail to disclose or suggest the use of the PDGF-B promoter for expression of any APP-related protein.

Mullan *et al.* disclose DNA encoding a form of APP770 having mutations at amino acids 670 and 671 and note that these mutations are associated with early-onset Alzheimer's disease. Mullan *et al.* also state (page 347, second column, first full sentence) that, based on the late onset of disease development in humans with the mutations, it is unlikely that transgenic animals having this mutation (or mutations at amino acid 717) would develop significant pathology.

Chartier-Harlin *et al.* disclose DNA encoding a form of APP having a mutation at amino acid 717 which is associated with familial Alzheimer's disease. Chartier-Harlin *et al.* fails to disclose or suggest use of this mutant in any transgenic animal.

Hendriks *et al.* disclose DNA encoding a form of APP having a mutation at amino acid 692 which is associated with familial Alzheimer's disease. Hendriks *et al.* fails to disclose or suggest use of this mutant in any transgenic animal.

None of Sasahara *et al.*, Mullan *et al.*, Chartier-Harlin *et al.*, or Hendriks *et al.* disclose or suggest any transgenic mouse producing the expression products recited in the claims at the recited levels.

B. The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). In rejecting a claim under 35 U.S.C. § 103, the Examiner must establish a *prima facie* case that: (i) the prior art suggests the claimed invention; and (ii) the prior art indicates that the invention would have a reasonable likelihood of success. *In re Dow Chemical Company,* 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Claims for an invention are not *prima facie*

obvious if the references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). Inherent, but unknown, features cannot support an obviousness rejection. "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Rijckaet*, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993).

C. The claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. However, none of the cited publications disclose or suggest transgenic mice producing the expression products recited in the claims at the required levels, and none disclose or suggest that the level of these expression products in a young mouse is predictive of the later development of Alzheimer's disease-related phenotypes such as plaques. As noted above, although there were numerous theories about which factors might be important for producing the most useful animal models of Alzheimer's disease, prior to applicants' discovery that high levels of certain expression products in brain tissue is a determinant for obtaining transgenic animals exhibiting characteristics relevant to Alzheimer's disease, it was not known which factors would in fact turn out to be important. Relevant to this, the Federal Circuit has stated that "[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The '742 patent fails to disclose or suggest the measurement of the recited expression products, or that a high level of these expression products might be correlated with development of amyloid plaques that stain with Congo red. The secondary references -- which, except for

Sasahara *et al.*, do not involve transgenic animals -- also fail to disclose or suggest the measurement of the recited expression products, or that a high level of these expression products might be correlated with development of amyloid plaques that stain with Congo red. Their combination with the '742 patent does not provide the critical teachings missing from the '742 patent. Thus, the cited publications, either alone or in combination, fail to teach or suggest all of the elements of the claimed mice.

The rejection asserts that the expression levels in the mice allegedly suggested by the combination of the cited publications would be expected to be the same as the claimed expression levels. Applicants disagree. It appears that the rejection is asserting that the expression levels would be inherent in the mice. As discussed above in connection with the rejections under 35 U.S.C. § 102, mice produced based on the cited publications would not inevitably produce the claimed expression and phenotype. There is no suggestion or motivation in the cited publications to even try to produce mice having the claimed expression levels, and no disclosure of how to achieve mice exhibiting Congo red staining. The cited publications simply fail to disclose or suggest these elements of the claimed mice. The importance of the claimed expression levels was not known until applicants' discovery of it. That which was not known cannot serve as the basis of obviousness. Applicants also note that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the cited publications. As a result, applicants' discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. An unidentified subset encompassed by a broad disclosure in a prior art document does not make obvious the subset. See *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

Accordingly, for all these reasons, the present claims are not obvious in view of the cited publications.

Regarding the propriety of combining the secondary teachings of the secondary publications with the primary references, applicants note that the focus of Sasahara *et al.* is on the study of PDGF expression and not on any possible use of the PDGF-B promoter. Thus, Sasahara *et al.* is non-analogous art with respect to transgenic animals and so is not properly combined with the U.S. Patent No. 5,387,742. None of the other publications disclose or suggest use of the PDGF-B promoter in transgenic animals for expression of APP-related genes. Mullan *et al.* state (page 347, second column, first full sentence) that it is unlikely that transgenic animals having this mutation (or mutations at amino acid 717) would develop significant pathology due to the late onset of disease development in humans with the mutations. Thus, Mullan *et al.* teaches away from the use of 717 or 670/671 mutations in transgenic animals. For these reasons, applicants assert that cited publications in combination fail to disclose or suggest the claimed transgenic mice and that no proper *prima facie* case of obviousness has been established. Accordingly, for all of the above reasons, the present claims are not obvious in view of the cited publications.

2. Claims 1, 2, 5-20, 26, 29, 30, 33-48, 53, and 56 were rejected under 35 U.S.C. § 103(a) as obvious in view of U.S. Patent No. 5,387,742. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,387,742 discloses transgenic animals containing constructs encoding, for example, APP770, APP751, and APP695, which serve as models of Alzheimer's disease. The present claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. U.S. Patent No. 5,387,742 does not

disclose or suggest a transgenic mouse that produces these expression products at the required level. Thus, U.S. Patent No. 5,387,742 fails to disclose or suggest each and every feature of the claimed mice.

The rejection asserts that the expression levels in the mice allegedly suggested by U.S. Patent No. 5,387,742 would be expected to be the same as the claimed expression levels. Applicants disagree. It appears that the rejection is asserting that the expression levels would be inherent in the mice. As discussed above in connection with the rejections under 35 U.S.C. § 102, mice produced based on the cited publications would not inevitably produce the claimed expression and phenotype. There is no suggestion or motivation in U.S. Patent No. 5,387,742 to even try to produce mice having the claimed expression levels, and no disclosure of how to achieve mice exhibiting Congo red staining. U.S. Patent No. 5,387,742 simply fails to disclose or suggest these elements of the claimed mice. The importance of the claimed expression levels was not known until applicants' discovery of it. That which was not known cannot serve as the basis of obviousness. Applicants also note that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the cited publications. As a result, applicants' discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. An unidentified subset encompassed by a broad disclosure in a prior art document does not make obvious the subset. See *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

Accordingly, U.S. Patent No. 5,387,742 fails to make obvious the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,387,742. The rejection provides no suggestion or motivation to modify the assay disclosed in U.S. Patent No. 5,387,742 to include

the recited markers. For this additional reason, U.S. Patent No. 5,387,742 does not make obvious claims 8, 10, 12, 14, 35, 37, 39, and 41.

3. Claims 3,14, 15, 25 and 26 were rejected under 35 U.S.C. § 103(a) as obvious in view of Games, et al., *Nature* 373:523-527 (1995). Claims 1-7, 10, 11, 14-16, 18, 19, 21, 22, 25 and 26 were rejected under 35 U.S.C. § 103(a) as obvious in view of U.S. Patent No. 5,811,633. Applicants respectfully traverse these rejections.

A. Games *et al.* disclose transgenic mice containing a construct combining APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8. Games *et al.* also disclose that the mice produce many phenotypes related to Alzheimer's disease, including markers of Alzheimer's disease such as Aβ. Games *et al.* also disclose (page 526, column 2, second paragraph) that numerous prior transgenic mice (containing different constructs) failed to exhibit such phenotypes.

The claims (1) require, *inter alia*, that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue, and (2) exclude the use of constructs that are a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8. However, Games *et al.* fail to disclose or suggest any transgenic mouse that both (1) has an APP-related construct other than a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8,[18] and (2) produces the expression products recited in the claims. Thus, Games *et al.* fails to disclose or suggest each and every feature of the claimed mice. Accordingly, Games *et al.* fails to make obvious the claimed mice.

[18] The Office Action erroneously indicates that the construct used in the mouse of Games *et al.* is encompassed by the present claims.

B. U.S. Patent Nos. 5,811,633 describes transgenic animals containing constructs encoding, for example, APP770, APP751, and APP695, which serve as models of Alzheimer's disease. As noted above, the claims require that the transgenic mouse produce specific expression products. However, the only transgenic mouse disclosed in U.S. Patent No. 5,811,633 that produces the expression products at the required level (that is, the mouse having the combination cDNA/genomic DNA APP construct[19]) is specifically excluded from the claims. Thus, U.S. Patent Nos. 5,811,633 fails to disclose or suggest each and every feature of the claimed mice.

The rejection asserts that the expression levels in the mice allegedly suggested by U.S. Patent Nos. 5,811,633 would be expected to be the same as the claimed expression levels. Applicants disagree. It appears that the rejection is asserting that the expression levels would be inherent in the mice. As discussed above in connection with the rejections under 35 U.S.C. § 102, mice produced based on the cited publications would not inevitably produce the claimed expression and phenotype. There is no suggestion or motivation in U.S. Patent Nos. 5,811,633 to even try to produce mice having the claimed expression levels. U.S. Patent No. 5,811,633 simply fails to disclose or suggest these elements of the claimed mice. The importance of the claimed expression levels was not known until applicants' discovery of it. That which was not known cannot serve as the basis of obviousness. Applicants also note that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the cited publications. As a result, applicants' discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. An

[19]The $A\beta_{tot}$, $A\beta_{1-42}$, APPα, APPβ, and Aβ-encoding mRNA expression of this mouse, which corresponds to the transgenic mouse described by Games *et al.*, is neither disclosed nor suggested in U.S. Patent No. 5,811,633.

unidentified subset encompassed by a broad disclosure in a prior art document does not make obvious the subset. See *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

Accordingly, U.S. Patent No. 5,811,633 fails to make obvious the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,811,633. The rejection provides no suggestion or motivation to modify the assay disclosed in U.S. Patent No. 5,811,633 to include the recited markers. For this additional reason, U.S. Patent No. 5,811,633 does not make obvious claims 8, 10, 12, 14, 35, 37, 39, and 41.

4. Claims 1, 2, 5-20, 24-26, 28-30, 33-48, 51-53, and 56 were rejected under 37 U.S.C. § 103(a) as obvious in view of U.S. Patent No. 5,612,486. Applicants respectfully traverse this rejection.

U.S. Patent No. 5,612,486 discloses transgenic animals containing a construct encoding APP having the Swedish mutation. The present claims require that the transgenic mouse produce $A\beta_{tot}$, $A\beta_{1-42}$, a combination of APP and APPα, APPβ, mRNA encoding the Aβ-containing protein, or a combination of these expression products at specific levels in brain tissue. U.S. Patent No. 5,612,486 does not disclose or suggest a transgenic mouse that produces these expression products at the required level. Thus, U.S. Patent Nos. 5,612,486 fails to disclose each and every feature of the claimed mice.

The rejection asserts that the expression levels in the mice allegedly suggested by U.S. Patent No. 5,612,486 would be expected to be the same as the claimed expression levels. Applicants disagree. It appears that the rejection is asserting that the expression levels would be inherent in the mice. As discussed above in connection with the rejections under 35 U.S.C. § 102, mice produced based on the cited publications would not inevitably produce the claimed

expression and phenotype. There is no suggestion or motivation in U.S. Patent No. 5,612,486 to even try to produce mice having the claimed expression levels, and no disclosure of how to achieve mice exhibiting Congo red staining. U.S. Patent No. 5,612,486 simply fails to disclose or suggest these elements of the claimed mice. The importance of the claimed expression levels was not known until applicants' discovery of it. That which was not known cannot serve as the basis of obviousness. Applicants also note that the claimed expression levels even if present would at best be present in a subset of the mice allegedly suggested by the cited publications. As a result, applicants' discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. An unidentified subset encompassed by a broad disclosure in a prior art document does not make obvious the subset. See *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994).

Accordingly, U.S. Patent No. 5,612,486 fails to make obvious the claimed mice.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent No. 5,612,486. The rejection provides no suggestion or motivation to modify the assays disclosed in U.S. Patent No. 5,612,486 to include the recited markers. For this additional reason, U.S. Patent No. 5,612,486 does not make obvious claims 8, 10, 12, 14, 35, 37, 39, and 41.

Double Patenting Rejections

1. Claims 1-20, 22-26 and 28-56 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 9-16 and 18-26 of U.S. Application Serial No. 09/149,856.

Applicants will consider filing a terminal disclaimer when allowable subject matter is indicated.

2. Claims 1-20, 22, 23, 26, 29-50, 53 and 54 were rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over claims 1-6 of U.S. Patent Nos. 5,811,633 and 5,720,936. Claims 1, 2, 5-20, 24-26, 28-30, 33-48, 51-53 and 56 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486 and claims 6 and 10-12 of U.S. Patent No. 5,604,102. Applicants respectfully traverse these rejections.

In an obviousness-type double patenting rejection the question is whether the claims of one application are obvious in view of the claims of another application. Generally, the analysis required to show such obviousness is the same the analysis required to show obviousness under 35 U.S.C. § 103 (*In re Braithwaite,* 379 F.2d 594, n.2 (C.C.P.A. 1967)). Thus, the question is whether it would have been obvious to modify the methods or compositions claimed in the copending applications to arrive at what is presently claimed.

It is noted that the claims of U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486, and 5,604,102 do not recite expression levels for Aβ-related expression products as required by the claims. Prior to applicants' discovery it was not known that the high expression levels of Aβ-related expression products in transgenic mice is related to the development of plaques closely related to those found in Alzheimer's disease. Accordingly, for at least this reason, an obviousness-type double patenting rejection is not appropriate over the cited patents.

The Office Action states that such expression levels are inherent in the mammals recited in the claims of U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486, and 5,604,102. As discussed above in connection with the rejections under 35 U.S.C. § 102, mice produced based on the cited publications would not inevitably produce the claimed expression and phenotype. There is no suggestion or motivation in the cited publications to even try to produce mice having the claimed

expression levels, and no disclosure of how to achieve mice exhibiting Congo red staining. The cited publications simply fail to disclose or suggest these elements of the mice used in the claimed method. The importance of the claimed expression levels was not known until applicants' discovery of it. That which was not known cannot serve as the basis of obviousness. Applicants also note that that presently claimed expression levels would at best be present in a subset of the mammals claimed in the cited patents, and that applicants' discovery of the significance of such previously unknown expression levels lends patentability to the presently claimed mice. See *In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994). For at least this reason, applicants are not claiming the same invention as claimed in U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486, and 5,604,102.

Applicants also note that at least present claims 8, 10, 12, 14, 35, 37, 39, and 41 are limited to markers not disclosed in U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486, and 5,604,102. The rejection provides no suggestion or motivation to modify the assays disclosed in U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486 to include the recited markers. For this additional reason, applicants are not claiming the same invention as claimed in U.S. Patent Nos. 5,811,633, 5,720,936, 5,612,486, and 5,604,102.

In the case of Patent Nos. 5,811,633 and 5,720,936, the present claims specifically exclude the constructs claimed in the '633 and '936 patents. For this additional reason, applicants are not claiming the same invention as claimed in Patent Nos. 5,811,633 and 5,720,936.

Response Under 37 C.F.R. § 1.78(c)

Claims 1-20, 22, 23, 26, 29-50, 53, and 54 were considered to be directed to an invention not patentably distinct from claims 1-6 of commonly assigned U.S. Patent No. 5,811,633, and claims 1-6 of commonly assigned U.S. Patent No. 5,720,936. Although applicants dispute this,

pursuant to 37 C.F.R. § 1.78(c) applicants state that Samuel Wadsworth, Benjamin Snyder, Cha-Mer Wei and Paul Leibowitz, inventors of the subject matter of the '633 and '936 patents, are prior inventors of that subject matter. However, as discussed above, applicants submit that the claimed transgenic mice are separate and distinct from those disclosed in the '633 and '936 patents.

Allowance of claims 1-20, 22-26, 28-58 is respectfully solicited.

Respectfully submitted,

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Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Teresa R. Spratt

Date: October 27, 2000

Appendix: Claims As Pending

1. (Amended) A method for testing compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell and a region encoding an Aβ-containing protein, wherein the promoter is operatively linked to the region,

wherein the region comprises DNA encoding the Aβ-containing protein, wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of

APP770, APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP695, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717,

wherein the Aβ-containing protein includes amino acids 672 to 714 of human APP,

wherein the region encoding an Aβ-containing protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8,

wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of brain tissue of the mouse when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of brain tissue of the mouse when it is two to four months old, APP and APPα combined are expressed at a level of at least 150 picomoles per gram of brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of brain tissue of the mouse when it is two to four months old, and/or mRNA encoding the Aβ-containing protein is expressed to a

level at least twice that of mRNA encoding the endogenous APP of the transgenic mouse in brain tissue of the mouse when it is two to four months old;

wherein the transgenic mouse develops plaques that stain with Congo red; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

2. (Unamended) The method of claim 1 wherein the Aβ-containing protein is selected from the group consisting of APP770; APP770 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP751; APP751 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; APP695; APP695 bearing a mutation in the codon encoding one or more amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, 717; a protein consisting of amino acids 646 to 770 of APP; a protein consisting of amino acids 670 to 770 of APP; a protein consisting of amino acids 672 to 770 of APP; and a protein consisting of amino acids 672 to 714 of APP.

3. (Unamended) The method of claim 2 wherein the DNA encoding the Aβ-containing protein is cDNA or a cDNA/genomic DNA hybrid, wherein the cDNA/genomic DNA hybrid includes at least one APP intron sequence wherein the intron sequence is sufficient for splicing.

4. (Unamended) The method of claim 1 wherein the promoter is the human platelet derived growth factor β chain gene promoter.

5. (Unamended) The method of claim 1 wherein the region further comprises DNA encoding a second protein, wherein the DNA encoding the Aβ-containing protein and the DNA

encoding the second protein are operative linked such that the region encodes an Aβ-containing fusion protein comprising a fusion of the Aβ-containing protein and the second protein.

6. (Unamended) The method of claim 5 wherein the second protein is a signal peptide.

7. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

8. (Unamended) The method of claim 7 wherein the protein is selected from the group consisting of Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1α, IL-1β, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1, lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100β, $cPLA_2$, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-B, IκB, NFκB, IL-8, MCP-1, MIP-1α, matrix metaloproteinases, 4-hydroxynonenal-protein conjugates, amyloid P component, laminin, and collagen type IV.

9. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

10. (Unamended) The method of claim 9 wherein the protein is selected from the group consisting of Cat D,B, protein kinase C, NADPH, C3d, C1q, C5, C4bp, C5a-C9, tau, ubiquitin, MAP-2, neurofilaments, heparin sulfate, chrondroitin sulphate, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glycosylation end products, amyloid P component, laminin, and collagen type IV.

11. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

12. (Unamended) The method of claim 11 wherein the protein is selected from the group consisting of nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, glutamine synthetase, glucose transporter, PPI kinase, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, ubiquitin, and apolipoprotein E.

13. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been administered, or by cells derived from the transgenic mouse to which the compound has been administered.

14. (Unamended) The method of claim 13 wherein the encoded protein is selected from the group consisting of growth inhibitory factor, Cat D,B, Neuronal Thread Protein, nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, heme oxygenase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-

1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), advanced glycosylation end products, receptor for advanced glycosylation end products, COX-2, CD18, C3, fibroblast growth factor, CD44, ICAM-1, lactotransferrin, C1q, C3d, C4d, C5b-9, gamma RI, Fc gamma RII, CD8, CD59, vitronectin, vitronectin receptor, beta-3 integrin, Apo J, clusterin, type 2 plasminogen activator inhibitor, midkine, macrophage colony stimulating factor receptor, MRP14, 27E10, interferon-alpha, S100β, $cPLA_2$, c-jun, c-fos, HSP27, HSP70, MAP5, membrane lipid peroxidase, protein carbonyl formation, junB, junD, fosB, fra1, cyclin D1, p53, NGFI-A, NGFI-B, IκB, NFκB, IL-8, MCP-1, MIP-1α, matrix metaloproteinases, 4-hydroxynonenal-protein conjugates, amyloid P component, laminin, and collagen type IV.

15. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

16. (Unamended) The method of claim 15 wherein the behavior is selected from the group consisting of behavior using working memory, behavior using reference memory, locomotor activity, emotional reactivity to a novel environment or to novel objects, and object recognition.

17. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or severity of the histopathology present in the transgenic mouse to which the compound has been administered.

18. (Unamended) The method of claim 17 wherein the histopathology marker is selected from the group consisting of compacted plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density, and neuropil abnormalities.

19. (Amended) The method of claim 1 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

20. (Unamended) The method of claim 1 wherein the marker is detected or measured using RT-PCR, RNase protection, Northern analysis, R-dot analysis, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

22. (Unamended) The method of claim 1 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

23. (Unamended) The method of claim 22 wherein the codon encoding amino acid 717 is mutated to encode Phe.

24. (Unamended) The method of claim 1 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and/or

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Leu, Tyr, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

25. (Unamended) The method of claim 24 wherein the codon encoding amino acid 670 is mutated to encode Asn, and/or the codon encoding amino acid 671 is mutated to encode Leu or Tyr.

26. (Amended) The method of claim 1 wherein the promoter mediates expression of the construct such that $A\beta_{tot}$ is expressed at a level of at least 30 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, $A\beta_{1-42}$ is expressed at a level of at least 8.5 nanograms per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APP and APPα combined are expressed at a level of at least 150 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, APPβ is expressed at a level of at least 40 picomoles per gram of hippocampal or cortical brain tissue of the mouse when it is two to four months old, and/or mRNA encoding the Aβ-containing protein is expressed to a level at least twice that of mRNA

encoding the endogenous APP of the transgenic mouse in hippocampal or cortical brain tissue of the mouse when it is two to four months old.

28. (Unamended) The method of claim 1 wherein the region encoding an Aβ-containing protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

29. (Unamended) The method of claim 7 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{1-40}$, $A\beta_{N3}(pE)$, $A\beta_{X-42}$, $A\beta_{X-40}$, $A\beta_{Insoluble}$, $A\beta_{Soluble}$, full length APP, APPα, APPβ, FLAPP+ APPα, the last 100 amino acids of APP, and the last 57 to 60 amino acids of APP.

30. (Unamended) The method of claim 17 wherein the Alzheimer's disease marker is selected from the group consisting of APP695, APP751, and APP770, and wherein the change in histopathology is a reduction in the amount of Alzheimer's disease marker localized in plaques and neuritic tissue.

31. (Unamended) The method of claim 1 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding the Aβ-containing protein.

32. (Unamended) The method of claim 30 wherein the intron is an APP gene intron.

33. (Unamended) A method for screening compounds for an effect on an Alzheimer's disease marker comprising

a) administering the compound to be tested to a transgenic mouse, or cells derived from the transgenic mouse, wherein the transgenic mouse has a nucleic acid construct stably incorporated into the genome, wherein the construct comprises a promoter for expression of the construct in a mammalian cell operatively linked to a region of the construct encoding a human amyloid precursor protein,

wherein the region of the construct encoding a human amyloid precursor protein is selected from the group consisting of APP770 cDNA; APP770 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations;

APP751 cDNA; APP751 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695 cDNA; the APP695 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695, APP751, or APP770 cDNA truncated at amino acid 671 or 685; APP cDNA truncated to encode amino acids 646 to 770 of APP; a combination cDNA/genomic APP gene construct; a combination cDNA/genomic APP gene construct bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; and a combination cDNA/genomic APP gene construct truncated at amino acid 671 or 685;

wherein Aβ is expressed at a level of at least 50 ng/g brain tissue in the transgenic mouse when the transgenic mouse is three months of age;

wherein the transgenic mouse develops plaques that stain with Congo red; and

detecting or measuring the Alzheimer's disease marker such that any difference between the marker in the transgenic mouse, or by cells derived from the transgenic mouse, and the marker in a transgenic mouse to which the compound has not been administered, or by cells derived from the transgenic mouse to which the compound has not been administered, is observed,

wherein an observed difference in the marker indicates that the compound has an effect on the marker.

34. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the amount of the protein present in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

35. (Unamended) The method of claim 34 wherein the protein is selected from the group consisting of Cat D,B, Neuronal Thread Protein (CSF), nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, calbindin, adenosine A1 receptors, choline

acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

36. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is a reduction or absence of the protein in plaques or neuritic tissue present in the transgenic mouse to which the compound has been administered.

37. (Unamended) The method of claim 36 wherein the protein is selected from the group consisting of Cat D,B, protein kinase C, NADPH, C3d, C1q, C5, C4bp, C5a-C9, tau, ubiquitin, MAP-2, neurofilaments, heparin sulfate, chrondroitin sulphate, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

38. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a protein and the observed difference is an increase or decrease in the enzymatic or biochemical activity of the protein in the transgenic mouse to which the compound has been administered, or in cells derived from the transgenic mouse to which the compound has been administered.

39. (Unamended) The method of claim 38 wherein the protein is selected from the group consisting of nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, glutamine synthetase, glucose transporter, PPI kinase, cytochrome oxidase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, ubiquitin, and apolipoprotein E.

40. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a nucleic acid encoding a protein and the observed difference is an increase or decrease in the amount of the nucleic acid present in the transgenic mouse to which the compound has been

administered, or in cells derived from the transgenic mouse to which the compound has been administered.

41. (Unamended) The method of claim 40 wherein the protein is selected from the group consisting of growth inhibitory factor, Cat D,B, Neuronal Thread Protein (CSF), nicotine receptors, 5-HT_2 receptor, NMDA receptor, α2-adrenergic receptor, synaptophysin, p65, glutamine synthetase, glucose transporter, PPI kinase, GAP43, cytochrome oxidase, calbindin, adenosine A1 receptors, choline acetyltransferase, acetylcholinesterase, glial fibrillary acidic protein (GFAP), α1-antichymotrypsin, α1-antitrypsin, C-reactive protein, α2-macroglobulin, IL-1, TNFα, IL-6, HLA-DR, HLA-A, D,C, CR3 receptor, MHC I, MHC II, CD 31, CR4, CD45, CD64, CD4, spectrin, tau, ubiquitin, MAP-2, apolipoprotein E, glycosylation end products, amyloid P component, laminen, and collagen type IV.

42. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a behavior and the observed difference is a change in the behavior observed in the transgenic mouse to which the compound has been administered.

43. (Unamended) The method of claim 42 wherein the behavior is selected from the group consisting of behavior using working memory, behavior using reference memory, locomotor activity, emotional reactivity to a novel environment or to novel objects, and object recognition.

44. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is a histopathology and the observed difference is a decrease in the extent or severity of the histopathology present in the transgenic mouse to which the compound has been administered.

45. (Unamended) The method of claim 44 wherein the histopathology is selected from the group consisting of compacted plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density, and neuropil abnormalities.

46. (Unamended) The method of claim 44 wherein the Alzheimer's disease marker is selected from the group consisting of APP695, APP751, and APP770, and wherein the change in histopathology is a reduction in the amount of the marker localized in plaques and neuritic tissue.

47. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is cognition and the observed difference is a change in the cognition of the transgenic mouse to which the compound has been administered.

48. (Unamended) The method of claim 33 wherein the marker is detected or measured using RT-PCR, ELISA, antibody staining, laser scanning confocal imaging, and immunoelectron micrography.

49. (Unamended) The method of claim 33 wherein the codon encoding amino acid 717 is mutated to encode an amino acid selected from the group consisting of Ile, Phe, Gly, Tyr, Leu, Ala, Pro, Trp, Met, Ser, Thr, Asn, and Gln.

50. (Unamended) The method of claim 49 wherein the codon encoding amino acid 717 is mutated to encode Phe.

51. (Unamended) The method of claim 33 wherein the codon encoding amino acid 670 is mutated to encode an amino acid selected from the group consisting of Asn and Glu, or the codon encoding amino acid 670 is deleted, and

wherein the codon encoding amino acid 671 is mutated to encode an amino acid selected from the group consisting of Ile, Lys, Glu, Val, and Ala, or the codon encoding amino acid 671 is deleted.

52. (Unamended) The method of claim 51 wherein the codon encoding amino acid 670 is mutated to encode Asn, and the codon encoding amino acid 671 is mutated to encode Leu.

53. (Unamended) The method of claim 33 wherein the Alzheimer's disease marker is selected from the group consisting of $A\beta_{tot}$, $A\beta_{1-42}$, $A\beta_{N3}(pE)$, $A\beta_{X-42}$, and $A\beta_{Insoluble}$.

54. (Unamended) The method of claim 33 wherein the construct further comprises an effective amount of at least one intron, wherein the effective amount of at least one intron is located in the region of the construct encoding a human amyloid precursor protein.

55. (Unamended) The method of claim 54 wherein the intron is an APP gene intron.

56. (Unamended) The method of claim 33 wherein the region encoding a human amyloid precursor protein does not consist of a combination of APP cDNA encoding exons 1-6 and 9-18 and genomic APP sequences encoding introns 6, 7 and 8, and exons 7 and 8.

57. (New) The method of claim 1 wherein the Aβ-containing protein consists of all or a contiguous portion of a protein selected from the group consisting of APP770 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, APP751 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717, and APP695 bearing a mutation in one or more of the amino acids selected from the group consisting of amino acid 669, 670, 671, 690, 692, and 717.

58. (New) The method of claim 33 wherein the region of the construct encoding a human amyloid precursor protein is selected from the group consisting of APP770 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP751 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; the APP695 cDNA bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; APP695, APP751, or APP770 cDNA truncated at amino acid 671 or 685; APP cDNA truncated to encode amino acids 646 to 770 of APP; a combination cDNA/genomic APP gene construct bearing a mutation in the codon encoding amino acid 669, 670, 671, 690, 692, 717, or a combination of these mutations; and a combination cDNA/genomic APP gene construct truncated at amino acid 671 or 685.